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28. (Amended) A composition of Claim ²³27 wherein the chimeric antibody [binds to the epitope of] competitively inhibits binding of TNF α to monoclonal antibody cA2.

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30. (Amended) A composition of Claim ²⁵29 wherein the chimeric antibody is monoclonal antibody cA2.

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31. (Amended) A method ~~[for] of~~ treating [or preventing a tumor necrosis factor-mediated] an autoimmune or inflammatory disease in an individual in need thereof comprising co-administering methotrexate and a tumor necrosis factor alpha antagonist to the individual, in therapeutically effective amounts.

REMARKS

The above amendments to the specification are made to correct obvious typographical errors. The amendments to the claims are made to avoid certain issues raised by the Examiner under 35 U.S.C. § 112 and to clarify that which Applicants regard to be the invention. The amendments do not introduce new matter. The Office action will now be addressed under separate headings.

Applicants' Claim for Priority

The Examiner grants the claims a priority date of the parent application, United States application Serial No. 08/690,775 (February 28, 1996). The Examiner goes on to state, however, that priority applications USSN 08/403,785 (filed October 6, 1993) and PCT/GB94/00462 (filed March 10, 1994) do not "support" the broader claims of the instant application, including "preventing a tumor necrosis factor-mediated disease", "preventing Crohn's disease", and "tumor necrosis factor-mediated disease". Applicants respectfully disagree. However, the observation is believed to be moot in light of the amendment to the claims. Particularly, the claims have been amended to recite

the claimed embodiments of the invention relating to treating autoimmune diseases and inflammatory diseases, such as rheumatoid arthritis and Crohn's disease. Other embodiments of the invention can, of course, be pursued in a continuation or divisional application. Applicants do not relinquish any rights to the subject matter defined in the original claims.

With regard to the remaining claims which recite characteristics of the preferred anti-TNF antibody, cA2, the claims are patentable even if the Examiner's determination of the effective filing date is correct.

Formal Drawings

The Examiner states that formal drawings and photographs were submitted which fail to comply with 37 C.F.R. 1.84.

Formal drawings in compliance with 37 C.F.R. 1.84 are being filed concurrently herewith. It is noted that the action does not appear to require submission of the Formal Drawings at this time. The subject application does not include photographs.

The Recitation of Trademarks .

The specification has been amended to correct spelling and trademark errors.

Objection to the Specification and Rejection of Claims 1-31 Under 35 U.S.C. § 112, First Paragraph

The specification has been objected to and Claims 1-31 rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not enable any person skilled in the art to use the invention. The Examiner states that it would require undue experimentation to practice the claimed methods and compositions with a reasonable expectation of success because of (1) the lack of predictability of the art; (2) the lack of established clinical protocols for effective anti-inflammatory therapies with anti-cytokine therapy commensurate in scope with the claimed methods and compositions; (3) the absence of a

specific and detailed description in the specification of how to effectively practice the claimed invention; and (4) the absence of working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting any TNF-mediated disease and preventing TNF-mediated disease with any TNF-specific antibody. It is noted that the scientific or technical basis for the Examiner's conclusions or beliefs has not been provided. Thus, it is difficult to discuss the particulars of these broad conclusions. In any event, Applicants respectfully disagree with this assessment.

To be enabling under 35 U.S.C. § 112, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). The Court of Appeals for the Federal Circuit has stated that "[n]othing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." Id.

When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement. Id.

The specification teaches that TNF-mediated diseases can be treated in an individual by co-administering methotrexate and a TNF antagonist to the individual in therapeutically effective amounts. Examples of the TNF-mediated diseases that can be treated are disclosed in the specification, for example, at page 8, line 25 to page 10, line 35. Examples of TNF antagonists that can be used in the claimed invention are provided in the specification, for example, at page 12, line 29 to page 35, line 11). Guidelines for route of administration and dosages are

provided in the specification, for example, at page 35, line 28 to page 39, line 26.

Applicants have exemplified the claimed methods using monoclonal anti-TNF α antibody cA2 in patients with active rheumatoid arthritis (see specification, e.g., Examples 1-3). Since antibodies generally function by antagonizing or otherwise inhibiting the activity of its cognate antigen (in this case TNF alpha), it is expected, based upon scientific reasoning, that the claimed methods work in the same manner using other anti-TNF α antibodies as well as other TNF α antagonists. It is also expected, based upon scientific reasoning, that the claimed methods work in the same manner for other autoimmune and inflammatory diseases, known to be mediated by TNF alpha.

Thus, Applicants respectfully submit that the guidance provided in the specification is sufficient to teach the skilled artisan how to use the claimed invention without undue experimentation. It is noted that Claims 7-9, 15-17, 23-25 and 28-30 further characterize the antibody (Claims 9, 17, 25 and 30 define the specific exemplified antibody) and that Claims 10-17 claim methods of treating rheumatoid arthritis (Claim 17 with the specific exemplified antibody). Claims 18-25 relate to methods of treating Crohn's disease (Claim 25 with the specific antibody), see United States Patent No. 5,656,272. Claims 26-30 are drawn to compositions of matter, for which the specification is at least enabling for its use in treating rheumatoid arthritis, based upon the clinical data provided.

The Examiner states that:

it is not clear that the skilled artisan could predict the efficacy of targeting any TNF-mediated disease or inflammatory disease with any TNF specific antibody and methotrexate. It is important to note that there are distinct differences in the cytokine requirements for particular types of inflammation. Applicant has not provided information or nexus information a priori that establishes the efficacy of the claimed invention for the treatment of any TNF-mediated disease by targeting any TNF. The specification does not teach how to extrapolate data obtained from anti-TNF α and

methotrexate on arthritis to the development of effective in vivo human therapeutic methods and compositions for any TNF-mediated diseases, commensurate in scope with the claimed invention.

Again, the scientific basis for the Examiner's conclusions have not been provided. However, the specification and claims recite diseases which belong to an art-recognized class, are known in the art, or are otherwise accepted by person skilled in the art, to be "mediated" by TNF alpha. The fact that the diseases listed are different from each other in its "cytokine requirements" is irrelevant to the issue. The relevant question is whether these diseases are characterized by TNF alpha activity. The Examiner does not apparently dispute this assertion. The claims and specification do not embrace the treatment or prevention of diseases where TNF alpha does not play an important role in the disease. Thus, the person of skill in the art would accept the assertions in the specification as true and enabling.

This objection clearly does not relate to many of the presently pending claims, including Claims 10-30, particularly claims drawn to the specific characteristics of the exemplified antibody, cA2 (Claims 14-17, 22-25, and 27-30) or cA2 itself (Claims 17, 25 and 30).

The Examiner states that:

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunosuppressive drugs can be species- and model-dependent, it is not clear that reliance on the clinical treatment of rheumatoid arthritis with multiple infusions with the anti-TNF antibody cA2 and methotrexate . . . accurately reflects the relative efficacy of any anti-TNF antibody or anti-TNF specificity as well as targeting any TNF-mediated diseases encompassed by the claimed methods and compositions.

Again, Applicants disagree with the conclusion. The Examiner has not provided the documentation apparently relied upon for this broad assertion. As such, it is difficult to rebut

the particulars the Examiner is considering in support of this conclusion. In any event, as the present specification provides clinical data of the claimed co-administration, the argument is not fully understood. In this instance, the use of antibodies in treating autoimmune diseases such as rheumatoid arthritis and Crohn's disease has been further supported by clinical data, as established by the enclosed U.S. Patent (U.S. Patent No. 5,656,272; attached as the Exhibit). There is no scientific reasoning provided by the Examiner which would suggest that the invention would not work with other members of the genus.

This also argument does not relate to many of the specific claims, as discussed above, particularly Claims 9, 17, 25, and 30.

The Examiner also states that:

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect . . .; (2) the protein may not reach the target area . . .; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use. . . . See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat. App. & Inter. 1992).

Again, the Examiner appears to ignore the clinical data provided in the specification. Certainly, the cited case law does not stand for the proposition that an applicant for patent must provide clinical studies for more than one species of a claimed genus. These vague and general possibilities of the fate of a therapeutic protein have been rebutted by evidence. No more should be required. Again, the objection does not relate to many of the dependent and specific claims, as discussed above.

The Examiner goes on to state in the rejection that:

Although in vitro experimental studies and animal models validate concepts based on studies of human disease, such studies are limited to the "acute" as opposed to "chronic" nature of the disease. In vitro assays are conducted under controlled conditions which do not necessarily reflect the complexity of in vivo conditions. In animal models, the onset of

inflammation is rapid with an aggressive destructive process, whereas in humans the disease progresses more slowly, often with natural periods of disease exacerbation and remission. Often the antagonist and the stimulus/insult are given at the same time. Immunosuppression is much easier to achieve under such controlled conditions than experienced in the human immunoregulatory diseases such as the acute and chronic immune diseases, autoimmune diseases, inflammatory diseases and neurodegenerative diseases targeted by the claimed invention. In human diseases, patients are treated generally after the onset of disease and not prior to disease.

These possibilities of difficulties which may be encountered in therapy have been rebutted by clinical evidence in patients after onset of chronic disease. Respectfully, many of the assertions presented in this argument are untrue. The argument as a whole does not consider the facts or evidence of the present application. Again, the argument does not relate to many of the dependent and specific claims.

The Examiner also states that:

There is insufficient information or guidance as to how to select those patients to "prevent" the onset of the various diseases encompassed by the claimed invention. There is insufficient information to determine which markers would be predictive of said diseases in order to treat patients prior to the onset of said diseases, as a preventive regimen.

Applicants respectfully disagree. However, in an effort to advance prosecution of the subject application, the claims have been amended to recite the treatment of disease.

The Examiner refers to an article authored by inventors of the present invention. It is agreed that Elliott et al. (*Arth. Rheum.*, 36(12):1681-1690 (1993)) disclose that the best specificity for treating arthritis is $\text{TNF}\alpha$, rather than $\text{TNF}\beta$. Thus, to eliminate issues in the present application, the claims have been amended to indicate that $\text{TNF}\alpha$ is the TNF specificity which is targeted.

Natanson et al. (*Ann. Int. Med.*, 120(9):771-783 (1994)) is cited as teaching that murine anti-TNF antibodies have not been

beneficial in treating cachexia and sepsis and that targeting TNF may be harmful. It is believed that the claims, as amended, avoid the issue.

The Examiner states that "there is insufficient guidance and direction as to the selection and enablement of any TNF antagonist." Applicants respectfully disagree with this assessment.

As defined in the specification, TNF antagonists decrease, block, inhibit, abrogate or interfere with TNF activity *in vivo*. (see, e.g., page 12, lines 30-32). Applicants disclose that such TNF antagonists include anti-TNF antibodies and receptor molecules which bind specifically to TNF, agents which prevent or inhibit TNF synthesis or TNF release, and agents which prevent or inhibit TNF receptor signalling (see specification, e.g., page 12, line 32 to page 13, line 14). Specific examples are provided as well. As the Examiner is undoubtedly aware, there are numerous TNF antagonists which are known in the art. As discussed above, since antibodies generally function by antagonizing or inhibiting the activity of its cognate antigen, it is expected, based upon scientific reasoning, that other agents which antagonize TNF can also be employed in the present invention. Further, the argument does not relate to many of the dependent and specific claims.

In view of the foregoing discussion, withdrawal of the objection to the specification and rejection of Claims 1-31 under 35 U.S.C. § 112, first paragraph is respectfully requested. Furthermore, in the event that the Examiner maintains one or more of the objections raised in the Office action, it is respectfully requested that each individual claim presented be considered separately.

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Objection to the Specification and Rejection of Claims 8-9, 16-17, 24-25 and 29-30 Under 35 U.S.C. § 112, First Paragraph

The Examiner has objected to the specification and rejected Claims 8-9, 16-17, 24-25 and 29-30 under 35 U.S.C. § 112, first paragraph, on the grounds that the specification fails to provide evidence that a cell line expressing cA2 is known and readily available to the public, reproducible from a written description, or deposited. Applicants respectfully disagree with this assessment.

Claims 8, 16, 24 and 29 have been amended to recite treatment with a chimeric antibody which competitively inhibits binding of TNF α to monoclonal antibody cA2 to further clarify the invention sought to be claimed. Claims 9, 17, 25 and 30 recite treatment with cA2.

The Court of Appeals for the Federal Circuit has stated that:

No deposit is necessary if the biological organisms can be obtained from readily available sources or derived from readily available starting materials through routine screening that does not require undue experimentation.

In re Wands, 8 U.S.P.Q.2d 1400, 1403 (Fed. Cir. 1988).

The Examiner notes that the subject application, at page 14, lines 9-16, incorporates by reference information on cA2 to other U.S. patent applications not listed as priority documents. In particular, the subject application incorporates by reference information on cA2 described in U.S. Application 08/192,093 (filed February 4, 1994), U.S. Application No. 08/192,102 (filed February 4, 1994) (now U.S. Patent No. 5,656,272), U.S. Application No. 08/192,861 (filed February 4, 1994) and U.S. Application No. 08/324,799 (filed October 18, 1994; allowed May 28, 1997) (see specification, page 14, lines 9-13).

U.S. Application No. 08/192,102 is now U.S. Patent No. 5,656,272 (issued August 12, 1997). Additionally, U.S. Application No. 08/324,799 was allowed on May 28, 1997.

The referenced U.S. patent applications disclose the cloning and recombinant expression of the cA2 monoclonal antibody, including the sequencing of the light and heavy chain variable regions. The referenced patent applications also provide significant description of the properties (e.g., glycosylation, epitopic specificity and affinity) of the chimeric anti-TNF α antibody cA2. With this information, screening of antibodies which have the same or similar properties is straightforward to one skilled in the art.

Thus, given the guidance presented in the referenced patent applications, it would be a routine matter for one skilled in the art to produce the monoclonal antibody cA2 and antibodies chemically and structurally similar to the cA2 antibody for use in the claimed invention. Therefore, the cA2 antibody is enabled by the present specification, in view of the incorporation by reference to these referenced applications and a deposit is not required.

In view of the foregoing amendments and discussion, withdrawal of this objection to the specification and rejection of the claims under 35 U.S.C. § 112, first paragraph is respectfully requested.

Rejection of Claims 1-3, 8, 16, 24, 29 and 31 Under 35 U.S.C. § 112, First and Second Paragraphs

Claims 1-3, 8, 16, 24, 29 and 31 have been rejected under 35 U.S.C. § 112, first and second paragraphs, for failing to describe the claimed invention in such full, clear, concise and exact terms as to enable the skilled artisan to make and use the claimed invention, and/or for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Certain claims have been amended in response to the rejection. As amended, the claims even more particularly point out and distinctly claim the subject matter which Applicants regard as the invention, thereby obviating this rejection under 35 U.S.C. § 112, first and second paragraphs.

As amended, the claims indicated include the following changes, made in response to specific rejections made by the Examiner:

A) Claims 1-3 are objected to as indefinite in the recitation of "tumor necrosis factor-mediated disease" because it is not clear "whether said diseases reads on any inflammatory condition wherein TNF is present, wherein TNF has a direct role in pathology or wherein TNF has an indirect role in pathology." The Examiner states that "[a]lthough TNF contributes to certain conditions associated with inflammatory diseases, an artisan would not necessarily classify these diseases as TNF-mediated diseases, but rather inflammatory diseases wherein TNF plays some role." The rejection is not understood. The originally presented claims embrace the treatment of diseases that are mediated by TNF. The fact that there may exist other diseases where TNF is present but not TNF-mediated is not relevant to the issue. The originally presented claims did not embrace the treatment of such diseases. In any event, in an effort to advance prosecution in the subject application, Claim 1 has been amended to recite "autoimmune or inflammatory disease", as suggested by the Examiner. In view of this amendment, this rejection is believed to be moot.

Claims 1-3 are also objected to as ambiguous "in the recitation of TNF since there are different members associated with TNF, and it is not clear whether any disease with any role played by any TNF falls into the metes and bounds of TNF-mediated disease." Claims 1-3 have been amended to recite "anti-tumor necrosis factor alpha antibody".

Support for these claim amendments is found in the specification, for example, at page 8, line 28 - page 9, line 3; page 9, lines 12-27; and page 13, line 15 - page 21, line 2). Support for these amendments is also found in the priority documents listed in the specification at page 1, lines 1-15. It is believed that the rejection is moot in view of the amendments to the claims.

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B) Claim 31 is objected to as indefinite in the recitation of TNF antagonist "because the characteristics of the 'antagonist' are not known." The Examiner states that the term "encompasses potentially thousands of different antagonists and it is not apparent from the disclosure which particular antagonists are being referred to." Applicants respectfully disagree with this assessment.

As defined in the specification, the term "TNF antagonist" refers to an antagonist that decreases, blocks, inhibits, abrogates or interferes with TNF activity *in vivo* (see, e.g., page 12, lines 30-32). Thus, a clear definition that would be readily understood by the skilled artisan has been provided in the specification. Applicants disclose that TNF antagonists include anti-TNF antibodies and receptor molecules which bind specifically to TNF, agents which prevent or inhibit TNF synthesis or TNF release, and agents which prevent or inhibit TNF receptor signalling (see specification, e.g., page 12, line 32 - page 13, line 14). Thus, the specification provides many examples of what is envisioned by the term. Thus, it is respectfully submitted that the term "TNF antagonist" is definite. The fact that the term may be considered by the Examiner to be "broad" or the fact that it potentially embraces "thousands" of compounds certainly does not support the argument that the claims are either vague or indefinite. See M.P.E.P. § 2173.04, "Breadth Is Not Indefiniteness."

The Examiner also states that:

There is insufficient direction or guidance provided to assist one skilled in the art in the selection of such "antagonists" nor is there evidence provided that such "antagonists" would be effective in inhibiting TNF either *in vitro* or *in vivo* It would require undue experimentation to produce all such possible antagonists without more explicit guidance from the disclosure. It would require undue experimentation to investigate all such antagonists. It appears that undue experimentation would be required of one skilled in the art to practice the claimed method using the teaching of the specification alone.

Applicants respectfully disagree for the reasons set forth above. Briefly, compounds within this class are known for use in the treatment of disease. Nothing more is required.

C) Claims 8, 16, 24 and 29 are objected to as indefinite in the recitation of "binds to the epitope of cA2" because "it is unclear whether the specificity is cA2 or to the particular epitope bound by cA2" and whether cA2 "refers to a specific antigenic determinant or the intention is for an antigen."

Claims 8, 16, 24 and 29 have been amended to delete the phrase "binds to the epitope of cA2". These claims have also been amended to recite that the chimeric antibody competitively inhibits binding of TNF α to monoclonal antibody cA2. Support for this amendment is found in the specification, for example, at page 18, lines 3-8. The person of skill in the art would not find the phrase to be indefinite.

The Examiner continues the rejection by stating that: antibodies that can inhibit the binding of the claimed antibody species may block said binding or other functional attributes via steric hindrance as well as via binding the same epitope. In addition, the claims recite "the epitope" which implies there is a particular epitope intended and antibodies can recognize more than one epitope. These phrases also read on small amino acid sequences encompassed by linear or conformational epitopes which are incomplete regions of the epitopes bound by the claimed TNF-antibodies.

While the Examiner's concerns relating to the terminology are not fully understood, it is believed that these concerns have been obviated by the claim amendments discussed above. Further, it is noted that the Examiner acknowledges that the specification provides "guidance as to the particular cA2-specific antibody species". Thus, given the guidance presented in the specification, it would be a routine matter for one skilled in the art to identify chimeric antibodies that competitively inhibit binding of TNF α to monoclonal antibody cA2.

Rejection of Claims 1-31 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-31 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The particulars of the rejection recited under (A) appear to repeat those raised in the above rejection. Certain claims have been amended in response to the rejection. Support for the claim amendments is found throughout the specification. No new matter has been added. As amended, the claims obviate much of this rejection under 35 U.S.C. § 112, second paragraph.

As amended, the claims indicated include the following changes, made in response to specific rejections made by the Examiner:

A) Claims 1-6, 10-14, 18-22, 26-27 and 31 are objected to as indefinite in the recitation of the phrase "tumor necrosis factor" because "it is not clear which TNF is intended." Claims 1-6, 10-14, 18-22 and 26-27 and 31 have been amended to recite "tumor necrosis factor alpha".

B) Claims 7, 15 and 23 are objected to as indefinite in the recitation of "about 87-108 and about 59-80" because "it is unclear what these numbers refer to." As suggested by the Examiner, Claims 7, 15 and 23 have been amended to clearly recite that "87-108" and "59-80" are amino acid residues and to incorporate the appropriate SEQ ID NOs. It is noted however, that the term "about" has long been accepted in claim drafting. It is not seen that the amendment to this claim alters the scope of the claim.

C) Claims 8, 9, 16, 17, 24, 25, 29 and 30 are objected to as indefinite in the recitation of "cA2" because "its characteristics are not known" and the term "is merely a laboratory designation which does not clearly define the claimed product". Applicants respectfully disagree with this assessment.

As stated in Applicants' specification (see, e.g., page 18, lines 8-13), chimeric monoclonal antibody cA2 has been defined and described in detail in, for example, U.S. Application No. 08/192,102 (now U.S. Patent No. 5,656,272). This reference provides significant description of the properties and methods for producing chimeric monoclonal antibody cA2, thereby clearly establishing that the characteristics of cA2 are known and that the term clearly defines a product. There is nothing inappropriate in employing a laboratory designation in a claim. Indeed, an Applicant is permitted to be his own lexicographer.

D) Claim 28 is objected to as indefinite in the recitation of "hTNFA" because "hTNF α " is the appropriate term for clarity and consistency. The amendment to Claim 28 obviates the rejection.

Rejection of Claims 1-31 Under 35 U.S.C. § 103

Claims 1-31 have been rejected under 35 U.S.C. § 103 as being unpatentable over Bender et al. in view of Elliott et al. (Arth. Rheum., 36(12):1681-1690 (1993); hereinafter "Elliott I"), Elliott et al. (Lancet, 344:1105-1110 (1994); hereinafter "Elliott II"), Flesch et al. (hereinafter "Herve, et al., after the first named author), Barrera et al. and Kozarek et al.

Applicants' invention relates to methods of treating an autoimmune or inflammatory disease (Claims 1-3, 5-9 and 31), rheumatoid arthritis (Claims 10-17) or Crohn's disease (Claims 18-25) in an individual comprising co-administering methotrexate and an anti-TNF α antibody (or, in the case of Claim 31, a TNF α antagonist) to the individual. Applicants' invention also relates to a composition comprising methotrexate and an anti-TNF α antibody (Claims 26-30). Claim 4 has been cancelled.

Teachings of the Cited References

Bender et al.

Bender et al. teach the use of a TNF production inhibiting compound of Formula II (disclosed in the reference) for treatment or prophylaxis of a disease state in a human which is exacerbated or caused by excessive or unregulated TNF production (e.g., rheumatoid arthritis and inflammatory bowel disease) (Bender et al., col. 21, l. 31-53; and col. 22, l. 60-65).

Bender et al. also teach the use of an IL-1 production inhibiting compound of Formula I (disclosed in the reference) for treatment or prophylaxis of a disease state in a human which is exacerbated or caused by excessive or unregulated IL-1 production (e.g., rheumatoid arthritis and inflammatory bowel disease) (Bender et al., col. 18, l. 45-48; and col. 18, l. 56-57).

Bender et al. do not teach or suggest treating autoimmune or inflammatory diseases in an individual by co-administering methotrexate and an anti-TNF α antibody (or other TNF α antagonist) to the individual. Bender et al. also do not teach or suggest a composition comprising methotrexate and an anti-TNF α antibody. Bender et al. do not even mention methotrexate or anti-TNF α antibodies.

Elliott I and Elliott II

Elliott I and Elliott II (coauthored by the inventors of the subject application) teach the use of chimeric monoclonal antibody cA2 in the treatment of patients with active rheumatoid arthritis.

Neither Elliott reference teaches or suggests treating rheumatoid arthritis (or other autoimmune or inflammatory diseases) in an individual by co-administering methotrexate and an anti-TNF α antibody (or other TNF α antagonist) to the individual. The cited Elliott references also do not teach or suggest a composition comprising methotrexate and an anti-TNF α antibody. The Elliott references do not mention methotrexate.

Herve et al.

Herve et al. report the results of a phase I-II multicenter pilot study assessing the clinical efficacy of a monoclonal anti-TNF α antibody (B-C7) in the treatment of patients with refractory severe acute graft-versus-host disease (aGVHD). Many of the patients in the study also received cyclosporine associated with methotrexate as an aGVHD prophylaxis. Herve et al. state that the results from the study show the possible efficacy of an anti-TNF α monoclonal antibody in severe refractory aGVHD. The clinical effect of the methotrexate as a prophylactic is not clearly discussed in the article.

The reference does not teach or suggest the co-administration of methotrexate and a TNF antagonist in the treatment of the disease.

Barrera et al.

Barrera et al. disclose in their abstract the use of low-dose methotrexate for treating patients with rheumatoid arthritis. They report that "three patients with highest values of stimulated IL-1 β and TNF showed a decrease of more than 50% after MTX" (Barrera et al., second sentence from end). Barrera et al. conclude that low-dose methotrexate treatment "seems to induce changes in IL-1 β and TNF production in some RA patients" (Barrera et al., last sentence). This, however, does not teach or suggest a method of treating rheumatoid arthritis (or other autoimmune or inflammatory diseases) in an individual comprising co-administering methotrexate and an anti-TNF α antibody (or other TNF α antagonist) to the individual. Barrera et al. do not even mention anti-TNF α antibodies (or other TNF α antagonists). Barrera et al. also do not teach or suggest a composition comprising methotrexate and an anti-TNF α antibody or other TNF antagonist.

Kozarek et al.

Kozarek et al. report the results of an open-label study of methotrexate treatment in patients with refractory inflammatory bowel disease, including Crohn's disease. They found that methotrexate induced clinical and histologic remission in some patients.

Kozarek et al. do not teach or suggest treating refractory inflammatory bowel disease in an individual by co-administering methotrexate and an anti-TNF α antibody (or other TNF α antagonist) to the individual. Kozarek et al. also do not teach or suggest a composition comprising methotrexate and an anti-TNF α antibody. Kozarek et al. do not mention anti-TNF α antibodies (or other TNF α antagonists).

The Combination of References

In support of the rejection, the Examiner states:

One of ordinary skill in the art at the time the invention was made would have been motivated to combine targeting the different elements contributing to inflammatory responses including those associated with arthritis and Crohn's disease. The art teaches that targeting TNF can all diminish the activity of inflammatory responses, including the use of either TNF-specific agents such as TNF-specific chimeric antibodies or an anti-inflammatory agent such as methotrexate. Combination therapies were well known in the art and both methotrexate and anti-TNF antibodies were shown to be effective in vivo.

Applicants respectfully disagree with the Examiner's conclusion that the claimed invention was obvious.

Combining the elements of separate references which do not themselves suggest the combination necessary to obtain a claimed invention is generally improper. ACS Hospital Systems, Inc. v. Montefiore Hospital, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984). A *prima facie* case of obviousness is established only if the teachings of the cited art would have suggested the claimed invention to one of ordinary skill in the art with a reasonable degree of certainty of successfully achieving the claimed

results. In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art, not in Applicants' disclosure. Id.

None of the cited references, nor their combination, teach or suggest, with a reasonable expectation of success, co-administration of methotrexate and an anti-TNF α antibody (or other TNF α antagonist) to an individual for treating rheumatoid arthritis, Crohn's disease or other autoimmune or inflammatory diseases. None of the cited references, nor their combination, teach or suggest compositions comprising methotrexate and an anti-TNF α antibody.

In addition, one of ordinary skill in the art would not have been able to predict, given the cited references, whether co-administration of methotrexate and an anti-TNF α antibody to an individual would be effective in methods for treating rheumatoid arthritis, Crohn's disease or other autoimmune or inflammatory diseases. That is, none of the cited references, nor their combination, teach the effective treatment of an individual with rheumatoid arthritis, Crohn's disease or other autoimmune or inflammatory diseases by co-administration of methotrexate and an anti-TNF α antibody.

Further, there is nothing in this record to support the Examiner's contention that "Combination therapies were well known in the art".

The Examiner goes on to state in the rejection that:

It was prima facie obvious to combine two compositions each of which is taught by [the] prior art to be useful for [the] same purpose in order to form a third composition that is to be used for [the] very same purpose; [the] idea of combining them flows logically from their having been individually taught in [the] prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980.

It is not seen that the cited case provides a *per se* rule that any combination therapy is obvious where the individual components have been suggested as useful individually.

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In any event, Applicants demonstrated the unexpected result that combination therapy with methotrexate and an anti-TNF α antibody produced a rapid and sustained reduction in the clinical signs and symptoms of the treated autoimmune disease (see specification, e.g., page 4, lines 2-8; and Example 2). Applicants also demonstrated the unexpected and dramatic result that combination therapy with methotrexate and a multiple dose regimen of an anti-TNF α antibody produced markedly superior results than the results obtained with each agent alone, particularly at low doses of methotrexate (see specification, e.g., page 4, lines 9-19; Examples 1-3). The magnitude of these results in the treatment of autoimmune or inflammatory disease could not have been reasonably predicted from the cited references, as illustrated in, for example, Figures 1A, 2A, 3A, 4A, 5A and Figure 7 of the specification.

Significant improvement of the combination therapy was observed even in comparison to where optimal dosages of anti-TNF α antibody were administered alone (see specification, e.g., Example 1). It is by now well settled that significant improvements in combination therapies can rebut a *prima facie* case of obviousness. See In re Kollman, 201 U.S.P.Q. 193 (C.C.P.A. 1979). See also MPEP § 716.02(a).

Further, there is nothing of record which would indicate that those of ordinary skill in the art would reasonably conclude that such a dramatic effect would be expected by combination therapy with a methotrexate and an anti-TNF α antibody (see specification, e.g., Example 1).

Indeed, the Examiner does not appear to consider the data presented in the specification at all in the rejection of the present claims.

In summary, the cited references, either alone or in combination, do not teach or suggest the claimed invention (compositions comprising a methotrexate and an anti-TNF α antibody or methods of treating an autoimmune or inflammatory disease in an individual comprising co-administering methotrexate and an

anti-TNF α antibody (or TNF α antagonist)). The cited references, either alone or in combination, do not provide a reasonable expectation that co-administration of methotrexate and an anti-TNF α antibody (or TNF α antagonist) to an individual would be effective in methods for treating an autoimmune or inflammatory disease. The cited references, either alone or in combination, also do not reasonably suggest that the unexpected and superior results achieved and described in the subject application were possible. Thus, withdrawal and reconsideration of this rejection under 35 U.S.C. § 103 are respectfully requested.

CONCLUSION

It is respectfully submitted that the claims are in condition for allowance. The Examiner is respectfully requested to reconsider the rejections and to withdraw them.

If the Examiner believes that a telephone conversation would be helpful in expediting the prosecution of this application, the Examiner is requested to call the undersigned at (617) 861-6240.

Respectfully submitted,



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